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Original article

Antibiotic treatment for 6 days versus 12 days in patients with severe cellulitis: a multicentre randomized, double-blind, placebo-controlled, non-inferiority trial

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ABSTRACT

Objectives: To investigate whether antibiotic treatment of 6 days' duration is non-inferior to treatment for 12 days in patients hospitalized for cellulitis.
Methods: This multicentre, randomized, double-blind, placebo-controlled, non-inferiority trial enrolled adult patients hospitalized for severe cellulitis who were treated with intravenous flucloxacillin. At day 6 participants with symptom improvement who were afebrile were randomized between an additional 6 days of oral flucloxacillin or placebo in a 1:1 ratio, stratified for diabetes and hospital. The primary outcome was cure by day 14, without relapse by day 28. Secondary outcomes included a modified cure assessment and relapse rate by day 90.
Results: Between August 2014 and June 2017, 151 of 248 included participants were randomized. The intention-to-treat population consisted of 76 and 73 participants allocated to 12 and 6 days of antibiotic therapy, respectively (mean age 62 years, 67% males, 24% diabetics); 38/76 (50.0%) and 36/73 (49.3%) were cured in the 12- and 6-day groups respectively (ARR 0.7 percentage points, 95%CI: −15.0 to 16.3). Cure rates were 56/76 (73.7%) and 49/73 (67.1%) with the modified cure assessment (ARR 6.6, 95%CI: −8.0 to 20.8). After initial cure without relapse, day 90 relapse rates were higher in the 6-day group (6% versus 24%, $p < 0.05$).
Conclusions: Given the wide confidence intervals, we can neither confirm nor refute our hypothesis that 6 days of therapy is non-inferior to 12 days of therapy. However, a 6-day course resulted in significantly more frequent relapses by day 90. These findings require confirmation in future studies.
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Introduction

Cellulitis is one of the most common infections leading to hospitalization [1]. This skin and soft tissue infection is characterized by a combination of varying degrees of erythema, oedema, warmth and tenderness. Most cases are caused by β-haemolytic streptococci or *Staphylococcus aureus*. In areas without endemic methicillin-resistant *S. aureus* (MRSA) the empirical antibiotic regimen consists of penicillinase-resistant β-lactam antibiotics such as flucloxacillin [2].

Increasing antimicrobial resistance rates are an incentive to try to effectively reduce antibiotic consumption. Recent studies have shown that common infections leading to hospitalization—such as community-acquired pneumonia, complicated urinary tract infections, and osteomyelitis—can be effectively treated with shorter courses of antibiotics [3–6].

Although most European guidelines regard 10–14 days (i.e. 12 days on average) of antibiotic therapy as standard of care for patients hospitalized for cellulitis, this recommendation is not evidence-based, and the optimal duration remains unknown [7,8]. One study in a primarily outpatient setting suggested that for uncomplicated cellulitis 5 days of levofloxacin was as effective as 10 days [9]. We aimed to investigate whether patients admitted to the hospital to receive intravenous antibiotic treatment for cellulitis would be as effectively treated with a 6-day course of flucloxacillin as with the standard 12-day course.

Patients and methods

Study design and participants

The Duration of ANtibiotic therapy for CEllulitis (DANCE) trial was a multicentre, randomized, double-blind, placebo-controlled non-inferiority trial, performed in three university hospitals and eight general hospitals in The Netherlands among hospitalized patients with cellulitis meeting all inclusion and exclusion criteria (see Supplementary Material: Methods). Cellulitis was defined as warmth, erythema and induration of the skin and/or subcutaneous tissue, with or without pain, and included erysipelas [10,11]. Written informed consent was obtained from all participants. Medical ethical approval was obtained from the Medical Ethical Committee of the Academic Medical Centre (no. 2013_252). Local institutional review boards approved the study for local execution. The study protocol and amendments are available online [12,13] (See Supplementary Material Table S1 for protocol amendments.). The trial is registered at clinicaltrials.gov (NCT02032654) and the Dutch trial register (NTR4360).

Procedures

Eligible patients were included within 72 h of admission for baseline assessments. Participants received 1000 mg flucloxacillin intravenously every 6 h, until stepdown to 500 mg flucloxacillin orally every 6 h at the treating physician's discretion. Physical examination was performed, including measurement of erythema surface area, assessment of symptoms with the cellulitis severity score (CSS) and patient-reported scores. The CSS is a descriptive symptom score, with seven items being scored on a 4-point scale, creating a total score between 0 and 21 (Supplementary Material Table S2) [9]. (See Supplementary Material: Methods for details).

Participants were assessed for randomization 5 days (±24 h) after admission. They were randomized if after 5 days their CSS had improved without switching antibiotics, they were afebrile, their blood cultures were negative, and the diagnosis was unaltered. Follow-up visits were performed 14 days (±24 h) and 28 days (±24 h) after admission. Compliance with study medication was determined by pill count at day 14. A follow-up by telephone was performed 90 days after admission. Participants not eligible for randomization were followed up by telephone.

Randomization and masking

Participants were randomized in a 1:1 ratio to either an additional 6 days of oral flucloxacillin, or matching placebo, for a total of either 12 or 6 days of flucloxacillin (see Supplementary Material: Methods). Participants, treating physicians and trial staff were masked to the assignment.

Outcomes

The primary outcome was cure by day 14 without relapse by day 28 in the intention-to-treat (ITT) population, which included all participants who were correctly randomized. Cure by day 14 was defined as the absence of pain and warmth and a reduction in erythema and oedema. Relapse was defined as the initiation of new antibiotics for cellulitis by non-trial physicians.

Secondary outcomes included a per-protocol analysis (PPA), (time to) relapse within 90 days, sequential visual analogue scores (VASs) of pain and oedema, the CSS over time, and cure without relapse using a modified cure assessment. We performed predefined subgroup analyses for diabetes status and CSS at baseline and on day 5. Serious adverse events (SAEs) were reported, with readmissions for cellulitis counted separately. A Data Safety Monitoring Board (DSMB) reviewed the study data, including unblinded access to the preliminary primary outcome, SAEs and deaths (see Supplementary Material: Methods).

Sample size calculation and data handling

Recent trials reached roughly 85% cure rates, so assuming a non-inferiority margin of 10%, we required 158 participants per group [14–16]. (See Supplementary Materials: Methods for the sample size calculation and data handling and reporting).

Results

Between August 26, 2014, and June 29, 2017, 1051 patients were assessed for eligibility; 574 were eligible, and 248 were included (Fig. 1). One hundred and fifty-one participants were randomly assigned to either 12 days (n = 77) or 6 days (n = 74) of flucloxacillin. Inclusion and randomization rates were lower than anticipated. One hundred and sixteen patients were ineligible due to physicians deviating from the guideline-recommended drug for reasons other than allergy, while 93 patients had already received more than 4 days of oral antibiotics; 145 eligible patients declined to participate for reasons which included concerns for comorbidity, fear of longer duration of incapacitation, children advising their parent not to participate due to frailty, and having little faith in short-duration therapy due to frequent recurrences. Main reasons for non-randomization were non-improvement after 5 days and withdrawn consent. After exclusion of two patients who were wrongfully randomized, 76 and 73 patients were included in the ITT population for the 12- and 6-day groups, respectively. Thirty-two months into the trial, the funding agency expressed concerns that the trial would not reach the target sample size due to the slower-than-expected inclusion rate, and was not prepared to allocate additional funding. As a result the trial ceased inclusion on June 29, 2017.

Baseline and demographic characteristics were balanced between groups (Table 1 and Supplementary Material Table S3). The

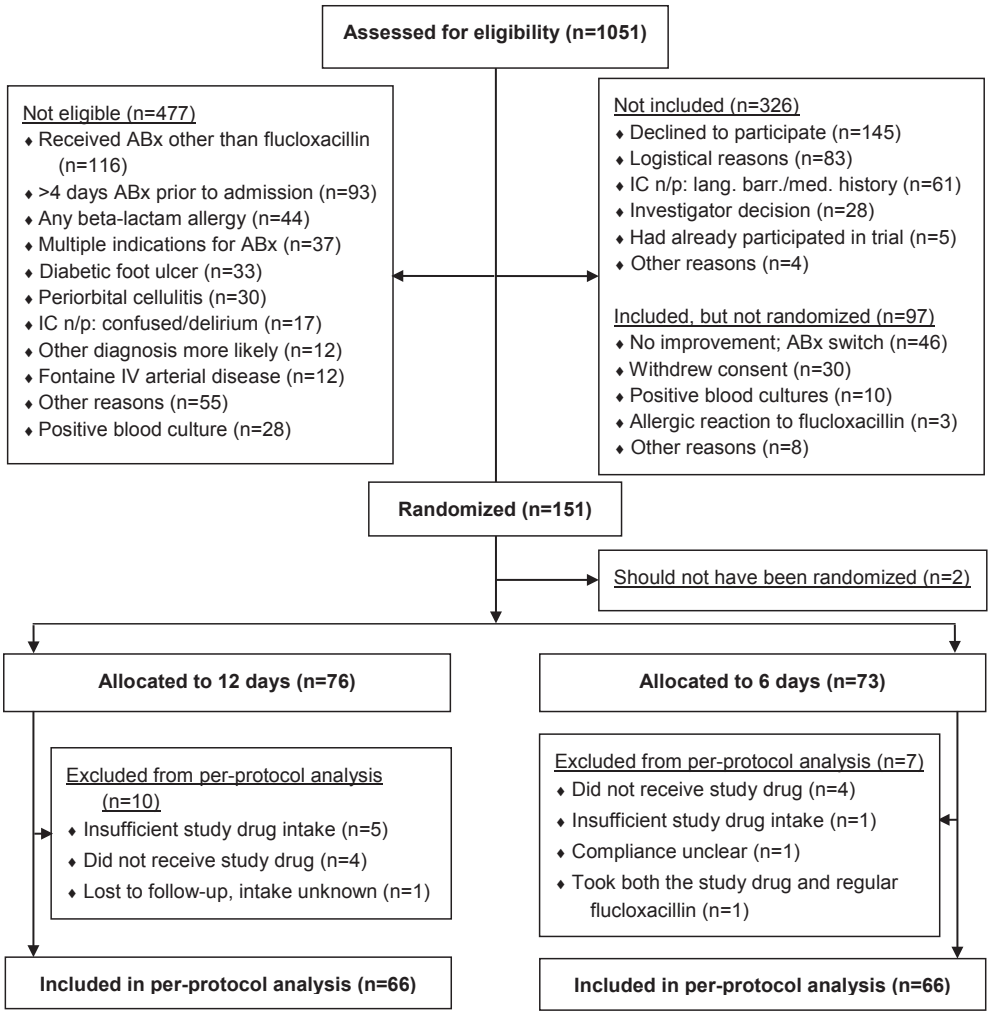

Fig. 1. Trial profile. ABx antibiotics. Participants were included during the first 72 h of admission. Participants were assessed for randomization 5 days (±24 h) after admission.

Table 1
Baseline characteristics on admission for the intention-to-treat population

	12-day group	6-day group
	$n = 76$	$n = 73$
Age, mean (sd)	63.1 (15.8)	61.9 (15.5)
Female, n (%)	25 (32.9)	24 (32.9)
Body mass index (BMI), median [IQR]	28.1 [24.8, 32.1]	29.0 [25.4, 33.9]
Obesity (BMI $\geq$ 30), n (%)	29 (38.2)	33 (45.2)
Diabetes, n (%)	18 (23.7)	18 (24.7)
Had cellulitis previously, *n* (%)	25 (33.3)	31 (42.5)
Tinea pedis, n (%)	34 (44.7)	30 (41.7)
Days with symptoms prior to admission, median [IQR]	2 [1,4]	2 [1,4]
Received antibiotics prior to admission, *n* (%)	26 (34.2)	32 (43.8)
Cellulitis location, *n* (%)		
Head	4 (5.3)	5 (6.8)
Arm	7 (9.2)	7 (9.6)
Leg	65 (85.5)	60 (82.2)
Trunk	0 (0.0)	1 (1.4)
Lymphadenopathy, *n* (%)	21 (27.6)	21 (28.8)
Fever, *n* (%)	39 (51.3)	31 (42.5)
Leucocytosis (defined as $>10 \times 10^9$/L), *n* (%)	54 (71.1)	51 (70.8)
C-reactive protein (mg/L), median [IQR]	104 [39, 175]	117 [49, 194]
Cellulitis severity score on admission, mean (sd)	8.4 (3.2)	8.5 (2.9)
Erythema surface area (cm^2), median [IQR]	755 [378, 1155]	916 [461, 1208]
Days on intravenous antibiotics, median [IQR]	3 [2,4]	3 [2,4]

mean age of the participants was 62 years; 67% were males, 24% had diabetes mellitus, and 42% were obese (BMI ≥30 kg/m^2). The severity of disease in the ITT population is reflected by a high mean CSS (8.4 ± 3.2 versus 8.5 ± 2.9 in the 12- and 6-day groups, respectively) and median erythema surface area (755 (378–1155) versus 916 (461–1208) cm^2) and high serum C-reactive protein levels (104 (39, 175) versus 117 (49, 194) μmol/L). The duration of intravenous antibiotic therapy before switching to oral antibiotic therapy was equal between groups: 3 (2–4) versus 3 (2–4) days.

As compared to non-randomized patients, randomized patients had at baseline a lower mean CSS (8.4 ± 3 versus 9.6 ± 2.5, p 0.012), median erythema surface area (792 (414–1207) versus 1057 (648–13590 cm^2, p 0.018), C-reactive protein level (108.5 (43.25–192.5) versus 183 (101–262) μmol/L, p < 0.001) and leucocyte count (12.2 (9.8–15.7) versus 14.2 (11.1–18.1) x 10^9, p 0.015) (Supplementary Material Table S4).

For the primary outcome, 38/76 participants (50%) were considered cured at day 14 without relapse by day 28 in the 12-day group, against 36/73 (49%) in the 6-day group (absolute risk reduction (ARR) 0.7, 95%CI −15.0 to 16.3) (Fig. 2). When applying our modified cure criteria, for which less stringent cure criteria were used, 56 (74%) of participants in the 12-day group were cured, against 49 (67%) in the 6-day group (ARR 6.6, 95%CI −8.0 to 20.8). In both scenarios we could not rule out a difference between groups in cure rates at day 14 as confidence intervals crossed the non-inferiority margin (Fig. 2). Imputation was needed for four patients and one patient in the 6- and 12-day groups respectively for the primary outcome, and six and three patients in the 6- and 12-day groups for the modified cure criteria. Modelling best- and worst-case scenarios for their outcomes did not alter the interpretation of the results.

In our per-protocol analysis, 29/66 (44%) and 34/66 (52%) of patients in the 12- and 6-day groups, respectively, were cured at day 14 with no relapse by day 28 (relative risk (RR) 1.2, 95%CI 0.7–1.7, p 0.49). Two (3%) and one (2%) patient outcomes were considered indeterminate. Using modified cure criteria, 51 (77%) versus 48 (73%) were cured, with one (2%) indeterminate outcome in the 6-day group (RR 0.9, 95%CI 0.8–1.1, p 0.69).

Of the patients in the 12- and 6-day groups who were cured according to the original definition in the ITT analysis, 2/35 (6%) and 8/34 (24%), respectively, had a relapse between day 28 and day 90 (RR 4.1, 95%CI 0.9–18.0, p 0.045). The Kaplan–Meier analysis, which takes censored data into account, showed a significant difference in relapse-free survival (log rank p 0.033) (Fig. 3). Of the two and eight patients, one and five already had a history of recurrent disease. Two patients (3%) and nine patients (13%) were readmitted for cellulitis in the 12- and 6-day groups, respectively (p 0.043).

No differences between groups were observed in patient-reported scores for pain and oedema or investigator-assessed CSS, except on day 3 (Fig. 4). Median length of stay was 4 days (IQR 3–6) in the 12-day group, and 3 days (IQR 3–5) in the 6-day group (p 0.25). Two deaths (1% total 30-day mortality) occurred in the 6-day group (0% versus 3%, p 0.46) (Cultures results and SAEs are listed in Supplementary Material Tables S5 and S6.). No SAE was attributed to trial interventions.

Eight patients (5%) in the ITT analysis had protocol deviations involving treatment duration prior to randomization. Two participants received less, and six received more, than the intended 6 days. In all cases deviations were ≤1 day. Compliance with trial medication was high, with 62 patients in both arms (82% and 85%) taking >80% of their allocated medication, and only six patients (4%; five in the 12-day group versus one in the 6-day group) taking <80% because of reasons other than reinitiation of unblinded antimicrobial therapy (four versus eight), adverse events (one versus none) or allergic reactions (one versus none).

Outcomes	12-day group (no./total no. (%))	6-day group (no./total no. (%))	ARR (95% CI)	RR (95% CI)	p
Primary outcome					
Cured without relapse	38/76 (50.0)	36/73 (49.3)	0.7 (-15.0 to 16.3)	1 (0.7 to 1.4)	1
Secondary outcomes					
Modified cure without relapse	56/76 (73.7)	49/73 (67.1)	6.6 (-8.0 to 20.8)	0.9 (0.7 to 1.1)	0.485
PPA, cured without relapse	29/66 (43.9)	34/66 (51.5)	-7.6 (-23.8 to 9.2)	1.2 (0.8 to 1.7)	0.486
Indeterminate outcome	2/66 (3.0)	1/66 (1.5)			
PPA, modified cure without relapse	51/66 (77.2)	48/66 (72.7)	4.5 (-10.2 to 19.0)	0.9 (0.8 to 1.1)	0.688
Indeterminate outcome	-	1/66 (1.5)			
Relapse after cure, day 90	2/35 (5.7)	8/34 (23.5)	-17.8 (-34.8 to -0.8)	4.1 (0.9 to 18)	0.045
Relapse after modified cure, day 90	4/51 (7.8)	11/44 (25.0)	-17.2 (-32.4 to -2.2)	3.2 (1.1 to 9.3)	0.026
Subgroup analyses					
Diabetes					
Yes	9/18 (50.0)	6/18 (33.3)	16.7 (-14.4 to 43.7)	0.7 (0.3 to 1.5)	0.5
No	29/58 (50.0%)	30/55 (54.5)	-4.5 (-22.1 to 13.5)	1.1 (0.8 to 1.6)	0.768

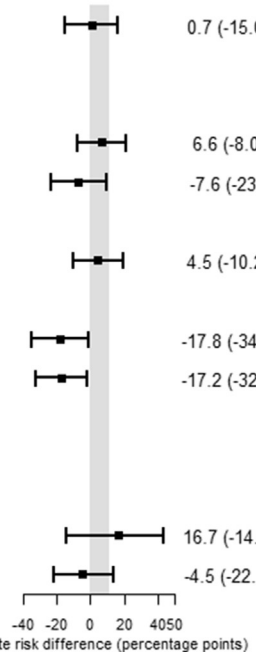

Fig. 2. Primary outcome, secondary outcomes, and sensitivity analyses for primary outcome. Grey bar indicates area between 0% (no difference) and 10% (non-inferiority margin). ARR, absolute risk reduction; PPA, per-protocol analysis; RR, relative risk. Denominators in relapse rates, cure rates and the Kaplan–Meier analysis in Fig. 3 do not necessarily match up due to missing data by day 90 and not imputing data for relapses.

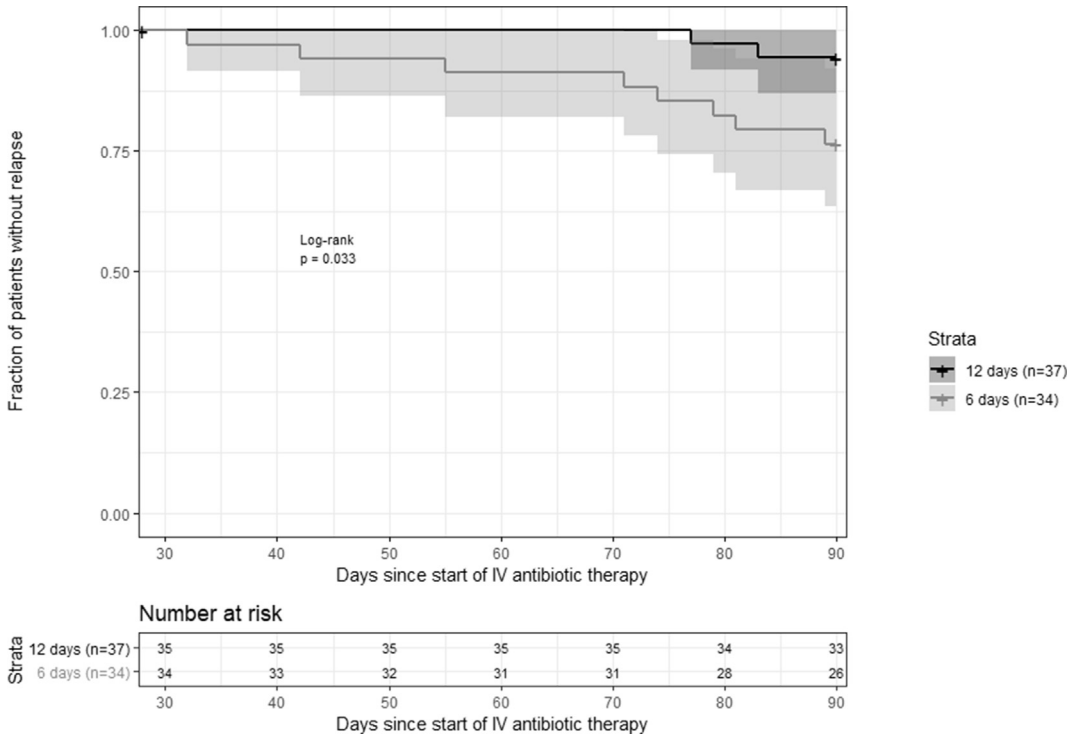

Fig. 3. Kaplan–Meier analysis of relapse-free survival after initial cure for primary outcome. Only patients deemed cured for the primary outcome are included in this analysis. Black indicates the 12-day group, grey indicates the 6-day group.

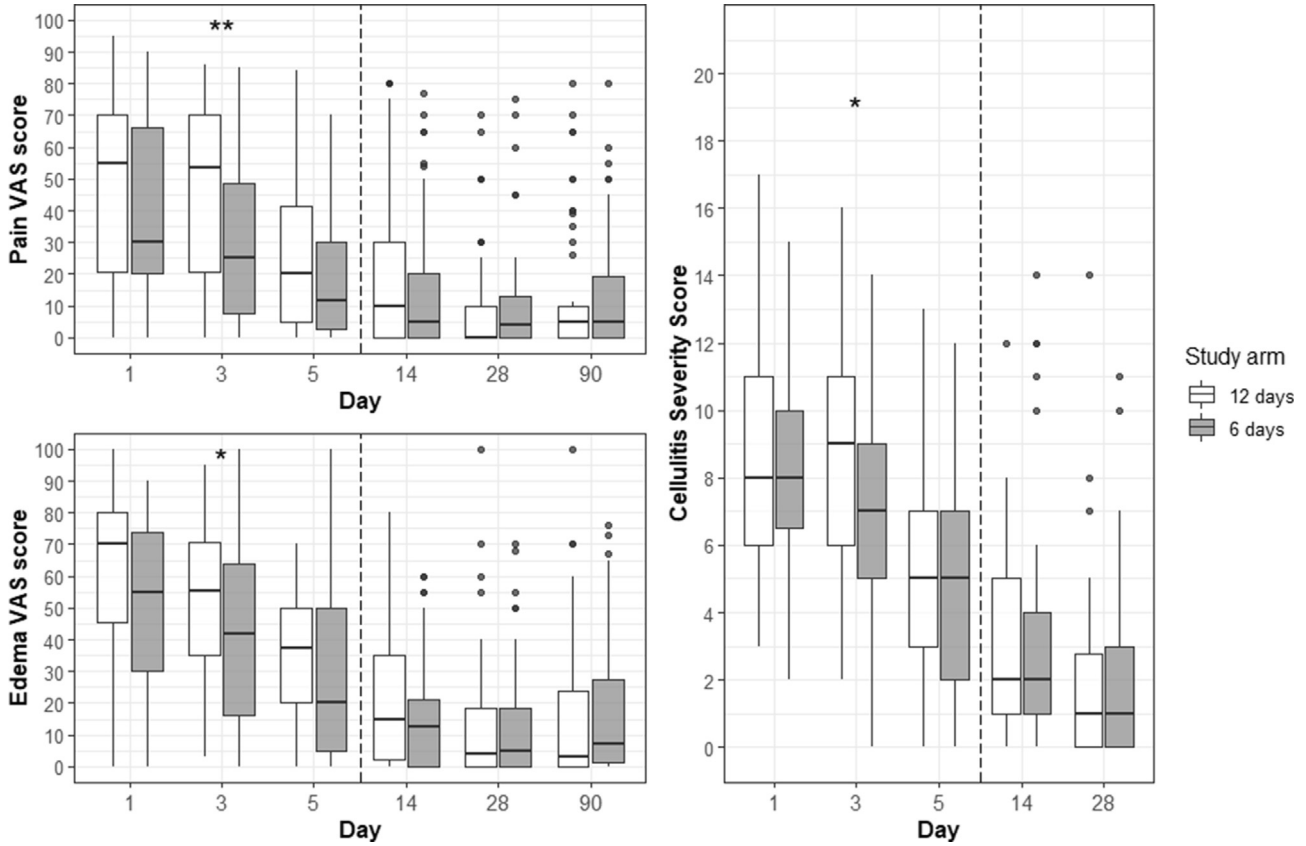

Fig. 4. Patient-reported and investigator-assessed symptom scores during follow-up. Bars indicate medians with interquartile ranges, whiskers extend to the lowest/highest value within 1.5 * IQR from the first/third quartile. The dashed line indicates the moment of randomization. VAS, visual analogue scale. *$p < 0.05$, **$p < 0.01$.

In this underpowered study, no significant differences in effectiveness were observed in the planned subgroup analyses, i.e., there were no interaction effects of cure without relapse with diabetes status (p 0.21) and CSS on the first day (p 0.83) or day 5 (p 0.87). Neither were there any interaction effects of non-significantly different baseline covariates, such as recurrent disease or antibiotic pretreatment, or treatment variables such as compliance or days on intravenous therapy.

Discussion

The results of this double-blind, randomized clinical trial show minimal absolute risk differences between 6 days and 12 days of antibiotic treatment in the occurrence of cure by day 14, without relapse by day 28. Non-inferiority, however, could not be claimed in this prematurely stopped trial due to the wide confidence interval crossing the 10% non-inferiority margin. However, participants with a 6-day course of antibiotic therapy showed more frequent relapses by day 90 after initial cure, and were more frequently readmitted. This indicates that perhaps not all patients can safely be treated with a shorter duration, although we found no statistically significant predictors for relapse. Conclusions are similar in per protocol analyses and with modified criteria for cure.

Prolonged antibiotic treatment of patients with an infection is likely a major source of selective pressure that drives antibiotic resistance development. Multiple trials comparing short-course with longer-course antibiotic therapy for a variety of infections have shown that short-course therapy is just as effective [3–6,17,18]. The only previous study on cellulitis treatment duration suggested the same for mild to moderately severe cellulitis, but this was in a primarily outpatient population and utilized a quinolone antibiotic [9]. It compared 5 and 10 days of levofloxacin, and reached remarkably high cure rates of 98%. Our results hint against using a short course of antibiotics in patients hospitalized for cellulitis, as in some patients a shorter antibiotic course appears to increase the chance of recurrent infection.

Owing to the fact that Dutch hospitals admit only the severest 7% of patients, the severity of disease in our cohort was high—as illustrated by the large erythema surface area and high median CRP and leucocyte values—compared to previous trials [2,9,14–16]. This was also reflected in the relatively low cure rates of just 50% in our primary endpoint analysis. Hypothesizing that this was the result of cure criteria that were too strict rather than disease severity, we changed the operationalization of the measured parameters for cure post-hoc (while still blinded; Supplementary Material Table S1). This increased cure rates to 75%. Cure rates in cellulitis trials have varied between 68% and 98%, although both timing and methods of cure assessment varied, and some trials also included cutaneous abscesses [9,14–16,19–22]. Of note, patients included in these studies generally presented with lower CRP and leucocyte concentrations and smaller lesion areas when compared to our population [14–16,19,20]. The relapse rate in our 12-day group is comparable with that of previous studies [23,24].

This study has limitations. Our data cannot be extrapolated to outpatients with mild infections, nor can it be generalized to all severe cellulitis patients. Furthermore, up to 30% of cellulitis diagnoses have been reported to be mimics [25]. Additionally, one has to be cautious about generalizing the results to antibiotics other than flucloxacillin. Our pragmatic design in which the duration of intravenous therapy was determined by the attending physician might skew data, as an early switch might influence cure rates, although this will have happened proportionally in both groups. Finally, because of logistical challenges, this study is underpowered for the primary outcome due to not reaching the target sample size. Nevertheless, the question remains whether no difference in the primary endpoint in a properly powered study would be sufficient to shorten therapy, when more relapses and readmissions occur.

This study also has several strengths, including its multicentre design and recruitment of a generalizable hospital population, that is, obese, elderly and ill in terms of comorbidity and inflammatory parameters. Participants were managed with the guideline-recommended drug. Randomization at day 5 reduces bias towards non-inferiority by filtering out patients with possible cellulitis mimics [25] and patients with pathogens intrinsically resistant to flucloxacillin. Bias towards non-inferiority is further reduced by high compliance and near-complete clinical follow-up of patients. Another strength is the use of multiple patient-reported and clinician-assessed outcomes, both short- and long-term [26].

The key challenge of cellulitis is the lack of a reference standard for diagnosis and cure [2]. Previous studies have used heterogeneous outcome assessments, both in terms of the timing of evaluation and with regard to cure criteria, often not reflecting what patients and clinicians feel is important [9,22,26–28]. A frequently used element in cure assessment is a decrease in erythema dimensions, with arguable clinical relevance, while other elements include varying degrees of resolution of varying symptoms, need for additional or alternative antibiotics, need for rehospitalization and emergency department visits, and mortality [22,27]. In line with the only other cellulitis treatment duration trial, we measured seven symptoms using a symptom severity scale (the cellulitis severity score [9]) set arbitrary borders, and combined it with the need for additional antibiotics at a later time point. Pilot studies on procalcitonin-guided therapy duration in cellulitis patients show conflicting results, so further biomarker studies are warranted [29,30].

In conclusion, given the wide confidence intervals, we can neither confirm nor refute our hypothesis that, for patients with severe cellulitis, 6 days of antibiotic therapy is non-inferior to 12 days of therapy. However, patients with a short course of therapy showed significantly more frequent relapses at day 90, and were more frequently readmitted for cellulitis. Additional studies are necessary to confirm these findings.

Transparency declaration

The authors declare no competing interests. This work was supported by a grant from The Netherlands Organization for Health Research and Development (ZonMW; grant number 836011024 to WJW).

Author contributions

WJW obtained funding for the study. DRC, BCO, AIMH, JMP and WJW developed the study design. All authors had access to the data gathered in their centres and take responsibility for the integrity of the data. DRC, JMP and WJW had full access to the data and take responsibility for the accuracy of the data analysis. DRC was responsible for data collection and performed the statistical analysis. All authors assisted with data interpretation. DRC performed the literature search and wrote the first draft of the paper. All authors have critically read and commented on draft versions of the report, and approved the final version.

Data sharing

This manuscript is one of several planned manuscripts based on the DANCE trial dataset. It is planned that all of the individual participant data collected during the trial, after de-identification, will be made available after publication of the last planned manuscript. Researchers can submit a methodologically sound

proposal to one of the corresponding authors. To gain access, data requestors will need to sign a data access agreement. No end date has been scheduled yet.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.09.019.

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